Menopause: The Journal of The North American Menopause Society
Vol. 26, No. 9, pp. 943-944
DOI: 10.1097/GME.0000000000001401
© 2019 by The North American Menopause Society

EDITORIAL

Physical function and age at natural menopause: two take-home messages

Victor W. Henderson, MD, MS

Natural menopause, the permanent end of menstruation and fertility, is associated with reduced ovarian functioning and lower levels of ovarian hormones. This normal physiological event has widespread health consequences.[1] Some such as loss of bone mass are obvious, but others can be harder to demonstrate with convincing certainty. Outcomes of natural menopause cannot be studied experimentally because an investigator cannot assign menopause to a group of women in the same way that a drug (eg, estradiol) or a lifestyle practice (eg, aerobic exercise) can be assigned. Investigators must perforce depend on observational research, which can address critical scientific questions not amenable to human experimentation but cannot establish causality. It is particularly difficult to disambiguate age-related changes remote from the time of menopause from those specifically consequent on menopause.

Among the changes that appear during midlife and extend into older adulthood, perhaps none is more important to health and quality of life than reduced physical function. Declining physical function is associated with disability and mortality.[2-4] Older men and women differ in the rate and extent of physical function decline,[5] and some of these differences may be biologically determined. To the extent that menopause plays a causal role, reductions in estrogens and other ovarian hormones are likely to be implicated, and progressively worse outcomes are predicted to accompany a progressively earlier age at menopause. If other biological factors or social factors are primary determinants of physical function after menopause,[6] age at menopause may not be relevant.

FIRST TAKE-HOME MESSAGE: THERE IS NO CLEAR RELATION BETWEEN AGE AT NATURAL MENOPAUSE AND PHYSICAL FUNCTION

In this issue, Velez et al[7] assess the relation between age at natural menopause and physical function measured at one time point using data from the Canadian Longitudinal Study on Aging (CLSA). This is a nationally representative cohort of volunteers aged 45 to 85 years enrolled between 2010 and 2013. Many participants provided two common measures of physical function, gait speed measured with the timed 4-m walk test and handgrip strength of the dominant hand measured with a dynamometer. Analyses involved over 9,000 women, who self-reported age at natural menopause, participated in one or both physical function tasks, and provided information on key variables.

Contrary to expectation, the overall results were null.[7] Analyses compared women whose natural menopause fell into one of five age brackets: menopause before age 40 years, 40 to 44 years, 45 to 49 years, 50 to 54 years (reference group), and after age 54. Primary findings failed to confirm the hypothesis that women who experienced natural menopause at later ages would perform better on either of the two physical performance tasks. These principal findings from the CLSA are consistent with those reported in some prior studies but not others. The null result of this observational analysis does not prove that age at menopause is irrelevant to physical function. Women in the CLSA differ from women in other cohorts and other populations, and CLSA results may not generalize to all women; or these findings may have occurred simply by chance. The primary take-home message is that there is, however, no clear relation between age at natural menopause and physical function measured by gait speed or hand grip, and perhaps there is no relation at all.

SECOND TAKE-HOME MESSAGE: PREMATURE MENOPAUSE IS DIFFERENT

In secondary analyses, the mean gait speed was slower in one small group of women compared with the reference group: women with premature menopause, defined as natural menopause occurring before age 40.[7] Even in this subgroup, the mean difference was small, only a tenth of a standardized unit (effect size −0.1, where effect size represents the difference between women in the premature menopause group and women in the reference group, divided by the standard deviation of the measurement; −0.032 m/s ÷ 0.22 m/s). Analysis of grip strength in the premature menopause group showed a similar difference (effect size −0.1; −0.41 kg ÷ 6.4 kg), although this difference was not significant. By way of comparison, effect sizes for women in the next earliest menopausal age group—the 40 to 45 year age group—were

Received June 20, 2019; revised and accepted June 21, 2019.
From the Departments of Epidemiology and of Neurology & Neurological Sciences, Stanford University, Stanford, CA
Funding/support: None reported.
Financial disclosure/conflicts of interest: None reported.
Address correspondence to: Victor W. Henderson, MD, MS, Stanford University School of Medicine, Stanford, CA.
E-mail: vhenderson@stanford.edu

Copyright @ 2019 The North American Menopause Society. Unauthorized reproduction of this article is prohibited.

0.0 m/s for gait speed (0.00 ÷ 0.22) and 0.0 kg (0.09 ÷ 6.39) for handgrip.

Most studies, including the CLSA, that have examined physical function in relation to menopausal age analyzed age as a categorical variable rather than as a continuous variable. If the critical determinant were length of time of ovarian hormone deprivation, then considering menopausal age continuously would provide greater power to discern a relation in support of the length-of-deprivation hypothesis. Looking for trends across age-at-menopause categories is an alternative, though less powerful, approach. No such trend is discernible in the CSLA results, although formal analyses are not provided.

Because health concerns and treatment guidelines sometimes differ for specific subgroups, analyses within strata defined by age brackets is reasonable when the intent is to reflect clinical practice parameters. Moreover, examining age strata can also reveal instances when health consequences of menopause affect a discrete subgroup differently.

Are women with premature menopause indeed different from other women with an early age at menopause in a way that is not reflected simply in their younger age? Some prior studies (eg, the National Health and Nutrition Examination Survey III[8]) that examined associations between age at natural menopause and physical function classified early menopause as menopause occurring before age 45 years. In the large CLSA, Velez et al[7] were able to distinguish women who reported premature menopause from those who reported menopause after age 40 and before age 45. Only 3.8% of CLSA women were classified as having premature menopause, and the prevalence in other populations is even less, only about 1%.[9]

Women with premature menopause not only face a more extended period of ovarian hormone loss, but they may differ in other, perhaps unique, ways that can affect physical function and health. In some instances, there is a genetic link. The best described genetic marker is fragile X associated primary ovarian insufficiency (FXPOI). Caused by abnormalities in the X-linked *FMR1* gene, usually expansion of a CGG triplet repeat, FXPOI is characterized by hypergonadotropic hypogonadism before age 40 years and oligomenorrhea or amenorrhea. The *FMR1* CGG triplet is normally repeated about 5 to 40 times. FXPOI is associated with 55 to 200 repeats. This premutation reduces levels of the *FRM1* protein product, leading to ovarian follicle dysfunction as well as other, somewhat variable manifestations. This disorder should be distinguished from fragile X syndrome, where the *FRM1* CGG segment is expanded more than 200 times, silencing the *FMR1* gene and leading to phenotypes that are quite different.

FXPOI is the most common genetic mutation associated with premature menopause, but only about 0.34% of women carry the *FRM1* premutation.[10] The proportion would, of course, be much higher among women with premature menopause. Rarer genetic conditions, autoimmune disorders, and other medical conditions are also associated with premature menopause.[11,12]

These considerations imply that women with premature menopause are in some ways distinct from other women. For most women with premature menopause, the cause cannot be pinpointed, but some of the underlying conditions affect other organ systems and may have health consequences that extend beyond a prolonged loss of ovarian hormones. Future studies of physical function and other health consequences of menopause should not look simply at age of natural menopause as a continuous variable but should also consider unique characteristics of the vulnerable population of women with premature menopause.

REFERENCES

1. Lobo RA, Davis SR, De Villiers TJ, et al. Prevention of diseases after menopause. *Climacteric* 2014;17:540-556.
2. den Ouden ME, Schuurmans MJ, Mueller-Schotte S, van der Schouw YT. Identification of high-risk individuals for the development of disability in activities of daily living. A ten-year follow-up study. *Exp Gerontol* 2013;48:437-443.
3. Rijk JM, Roos PR, Deckx L, van den Akker M, Buntinx F. Prognostic value of handgrip strength in people aged 60 years and older: a systematic review and meta-analysis. *Geriatr Gerontol Int* 2016;16:5-20.
4. Veronese N, Stubbs B, Volpato S, et al. Association between gait speed with mortality, cardiovascular disease and cancer: a systematic review and meta-analysis of prospective cohort studies. *J Am Med Dir Assoc* 2018;19:981-988.e987.
5. Gordon EH, Peel NM, Samanta M, Theou O, Howlett SE, Hubbard RE. Sex differences in frailty: a systematic review and meta-analysis. *Exp Gerontol* 2017;89:30-40.
6. Kuh D, Hardy R, Blodgett JM, Cooper R. Developmental factors associated with decline in grip strength from midlife to old age: a British birth cohort study. *BMJ Open* 2019;9:e025755.
7. Velez MP, Alvarado BE, Rosendaal N, et al. Age at natural menopause and physical functioning in postmenopausal women: the Canadian Longitudinal Study on Aging. *Menopause* 2019;26:958-965.
8. Tom SE, Cooper R, Patel KV, Guralnik JM. Menopausal characteristics and physical functioning in older adulthood in the National Health and Nutrition Examination Survey III. *Menopause* 2012;19:283-289.
9. Okeke T, Anyaehie U, Ezenyeaku C. Premature menopause. *Ann Med Health Sci Res* 2013;3:90-95.
10. Hunter J, Rivero-Arias O, Angelov A, Kim E, Fotheringham I, Leal J. Epidemiology of fragile X syndrome: a systematic review and meta-analysis. *Am J Med Genet A* 2014;164a:1648-1658.
11. Jiao X, Zhang H, Ke H, et al. Premature ovarian insufficiency: phenotypic characterization within different etiologies. *J Clin Endocrinol Metab* 2017;102:2281-2290.
12. Persani L, Rossetti R, Cacciatore C. Genes involved in human premature ovarian failure. *J Mol Endocrinol* 2010;45:257-279.

© 2019 The North American Menopause Society

Copyright @ 2019 The North American Menopause Society. Unauthorized reproduction of this article is prohibited.